

**Remarks**

Claims 1-3, 7, and 16-23 were pending prior to this Response. By the present communication, claims 24-28 have been added, no claims have been canceled, and claims 1, 17, and 22 have been amended to define Applicants' invention with greater particularity. Support for the newly added and amended claims may be found throughout the specification and claims as originally filed and at page 3, lines 15-16; page 9, lines 3-14; page 10, line 29; page 15, line 5; page 15, lines 9-14 and 33-34; page 16, lines 7-17; and page 38, lines 8-22 of the specification. Accordingly, upon entry of the present amendment, claims 1-3, 7, and 16-28 will be pending in this application.

**Objection to the Claims**

The Office Action objects to claim 22 on the basis of an alleged informality. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 22 as suggested by the Examiner.

Withdrawal of the objection is respectfully requested.

**Rejections under 35 U.S.C. § 102**

Applicants respectfully traverse the rejection of claims 1-2, 7, 16, and 22-23 under 35 U.S.C. §102(b) as allegedly being anticipated by Domenighini et al. (WO 93/13202; hereinafter, "Domenighini") in light of extrinsic evidence provided by Rappuoli (US 20040028690; hereinafter "Rappuoli") or Barchfield (US 20050106180; hereinafter "Barchfield"). Applicants respectfully draw the Examiner's attention to the apparent typographical error in the Office Action, which associates U.S. Patent Application No. 20050106180 filed on May 19, 2005 with Rappuoli et al. and submit that Barchfield et al. are inventors of the same. To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131.

The Office Action alleges that although the toxins of Domenighini were obtained by a

different process they are equivalent to the claimed toxins because Domenighini discloses the same or equivalent positions for mutation as recited in the instant claims. In view of the fact that Domenighini does not disclose toxin adjuvanticity, the Action invokes Rappuoli and Barchfield and alleges that these references provide extrinsic evidence that the toxins of Domenighini would inherently possess adjuvant activity.

Applicants respectfully submit that the claimed toxins are necessarily distinct from the toxins of Domenighini given that Domenighini does not at any point disclose chemical attenuation of its toxins much less incubation of the toxins with formalin, therefore, the toxins produced by the Domenighini method could not be bound to formaldehyde at the lysine residues. In contrast, the process as recited in claim 1 results directly in an adjuvant comprising a purified and attenuated toxin, wherein the lysine residues of the same toxin are bound to formaldehyde as a consequence of a formalin incubation period. The toxin produced by the method of the above-identified application is an entirely different chemical entity than the toxin of Domenighini and would have a different chemical formula and different physical properties. Moreover, binding of the lysine residues in a protein to a chemical moiety would affect the secondary and tertiary structures and necessarily the characteristics of the protein/toxin, which would have far-reaching consequences not restricted to toxicity alone. It is irrelevant that the toxins of Rappuoli allegedly possess adjuvanticity given that the recombinant toxins of Domenighini are inherently different from the claimed chemically attenuated formaldehyde-bound toxins. In view of the foregoing, Applicants' submit the rejection of claim 1, and claims dependent therefrom, is improper and respectfully request it be withdrawn.

Applicants respectfully traverse the rejection of claims 1-2, 16, and 22-23 under 35 U.S.C. §102(b) as allegedly being anticipated by Tang et al. (*Infection and Immunity*, 62(8), pp. 3299-3304; hereinafter, "Tang"). To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131.

The Office Action alleges that while Tang does not disclose an adjuvant, it discloses a purified and attenuated *Vibrio parahaemolyticus* thermostable hemolytic toxin that is similar or

equivalent to the product recited in the instant claims. The Action further alleges that the claimed attenuated toxin has the same inherent characteristics as the toxin disclosed in Tang.

Applicants respectfully submit that, in a similar fashion as the toxins produced by Domenighini, it is axiomatic that the attenuated toxins of Tang are different from the toxins recited in the instant claims. As with Domenighini, Tang's method does not entail chemical attenuation of its toxins, much less exposure to formalin thus it would be impossible to obtain a toxin having lysine residues bound to formaldehyde as recited in independent claim 1 by using the method of Tang. The discussion plied by the Applicants pertaining to the distinguishable nature and physical properties of the Domenighini toxins as compared to the claimed toxins apply equally to the Tang toxins. Whether or not the toxins produced by Tang inherently possess adjuvant activity is not germane given that Tang utilizes a recombinant method that results in chemically untreated attenuated toxins whereas the claimed method produces chemically attenuated toxins, and in particular toxins bound to formaldehyde at the lysine residues of the protein. Accordingly, Applicants' respectfully submit that the rejection is improper and request it be withdrawn.

Applicants respectfully traverse the rejection of claims 1 and 3 under 35 U.S.C. §102(e) as allegedly being anticipated by Ulrich et al. (US 6, 399, 332; hereinafter, "Ulrich"). To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131.

The Office Action alleges that Ulrich discloses purified and attenuated mutant SEA and SEB, wherein "[a]ll protein preparations were > 99% pure." The Action further alleges that the reference discloses "formalin treated natural SEB toxoid, the SEB (staphylococcus Beta toxin) [sic] is a protein treated with formalin to attenuate the toxin..." The Action concludes, based on the foregoing phrases, that Ulrich allegedly anticipates the claimed invention.

Applicants respectfully submit that when taken in context the excerpt quoted by the Action "[a]ll protein preparations were > 99% pure" clearly refers exclusively to the SEA-containing fractions (in which SEA is a genetically engineered super antigen) and do not include wild-type toxins or toxoids. Pursuant to Ulrich at column 2, lines 4-5 "the yields of toxin from

bacterial strains used for making toxoid are often low,” thus the term “toxoid” according to Ulrich clearly refers to attenuated toxin made from wild-type toxin bacterial strains and not genetically engineered toxins. Thus Ulrich itself indicates that the toxins produced by the disclosed method are inherently different than those produced by the claimed process i.e., *via* toxin made from wild-type bacterial strains. Indeed, Ulrich does not disclose how to obtain and purify wild-type toxins or toxoids, therefore the chemically attenuated toxin referred to by the Examiner at column 28, Example 9 is not the same product as that generated by the instant claims. Accordingly the rejection is improper and Applicants respectfully request it be withdrawn.

Applicants respectfully traverse the rejection of claims 1-3, 16-23 under 35 U.S.C. §102(b) as allegedly being anticipated by Fujita et al. (US 5, 101, 019; hereinafter, “Fujita”). To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131.

The Office Action alleges that Fujita describes “a purified and attenuated pertussis toxin, wherein the natural toxin was purified toxin...[t]he formulation incubation temperature was 39 °C” and references Example 1 of the reference. The Action concludes that, while Fujita does not disclose toxins possessing adjuvant activity, Pizza et al. (EP 0396964; hereinafter, “Pizza”) “carried out the same or equivalent methods steps and produced the same or equivalent mutated/attenuated [p]ertussis toxin as now claimed. Inherently [Fujita] anticipates the now claimed invention.”

Applicants respectfully submit that according to Fujita in Example 1, the endotoxin is removed from a fluid containing the anti-infective fraction and endotoxin of strains of phase I *Bordetella pertussis* and the fluid is detoxified with formalin. The starting fluid of Fujita contains filamentous hemagglutinin (FHA), pertussis toxin, and endotoxin. Example 1 indicates that the fraction lean in ET and rich in FHA was subjected to detoxification thus Fujita does not disclose isolation, purification, and detoxification of pertussis toxin alone. With regard to claim 1, and claims dependent therefrom, the method of Fujita would not lead to the same product obtained from the process as recited in claim 1. Furthermore, the method of Fujita does not

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disclose each and every element of the claimed method as recited in claim 17. In view of the foregoing, the issue of inherent adjuvanticity, allegedly provided by Pizza, or lack thereof in Fujita is irrelevant. Applicants respectfully submit that Fujita does not anticipate the instant claims for reasons discussed above and accordingly, request the rejection be withdrawn.

Applicants respectfully traverse the rejection of claims 1-2, 7, 16-18, and 20-23 under 35 U.S.C. §102(b) as allegedly being anticipated by Pizza in light of extrinsic evidence provided by Rappuoli et al. (US 2002/0187154; hereinafter “Rappuoli [‘154’].

Without acquiescing to the reasoning provided by the Office, and in order to expedite prosecution of the above-identified application, claims 1, 17, and 22 have been amended by Applicants to no longer recite “a mutant pertussis toxin.” As such, Applicants submit that Pizza is no longer available as prior art against the claimed invention. Withdrawal of the rejection is respectfully requested.

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**Conclusion**

In summary, for the reasons set forth herein, Applicants maintain that the claims clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to contact the undersigned so that a prompt disposition of this application can be achieved.

No fee is deemed necessary in connection with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees that are required, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,



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